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Effects of shallomin and podophyllin solution 25% for genital HPV warts in women: a randomized controlled trial

Shadab Shahali[1], Mansour Amin[2,3]✉, Masoumeh Khajeh Hassani[4], Reza Yaghoobi[5], Morteza Saki[3,6]

[1]*Department of Reproductive Health and Midwifery, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran*

[2]*Infectious and Tropical Diseases Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

[3]*Department of Microbiology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

[4]*Department of Midwifery, Reproductive Health Promotion Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

[5]*Department of Dermatology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

[6]*Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

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ABSTRACT

Objective: To compare the effect of shallomin (pure fraction of *Allium hirtifolium*) with podophyllin 25% solution on external genital human papillomavirus warts in women.

Methods: This study was a randomized controlled trial which was performed on two groups of 25 Iranian women with external genital warts at Imam Khomeini Hospital in Ahvaz, Iran. In the first group, shallomin was used once a day for six weeks at home. In the second group, 25% podophyllin solution, was applied on the lesion once weekly for six weeks.

Results: Shallomin and podophyllin resulted in wart clearance in 13/23 (56.5%), and 12/24 (50%) of patients, respectively. The clearance rate for shallomin was not significantly different from that of podophyllin (P=0.082). Six weeks after the treatment, the sizes of the lesions in the shallomin group and the podophyllin group decreased by (1.43±0.53) mm and (1.64±0.70) mm, respectively.

Conclusion: Shallomin is an effective treatment for genital warts, with similar efficacy to that of podophyllin.

1. Introduction

External genital warts are the most common sexually transmitted viral infection in the world, which is caused by human papillomavirus (HPV), and it can result in cervical cancer[1]. It is estimated that approximately 75% of sexually active women with HPV were infected with external genital warts[2]. There are more than 100 types of the viruses, including about 30 to 40 strains that can infect human genital tract. The oncogenic or high-risk types of HPV including 16, 18, 31, 33, 35, 39, 45, 51, 52, and 58 are associated with cervical, vulvar, vaginal, and anal cancers; and non-oncogenic or low-risk types (6, 11, 40, 42, 43, 44, and 54) are associated with genital warts[2,3].

So far, no definitive therapy has emerged as the ideal standard of care in the treatment of genital warts, and the therapy selection generally base on a patient-specific manner[2]. Therefore, the goal

✉Corresponding author: Mansour Amin, Infectious and Tropical Diseases Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Department of Microbiology, Ahvaz Jundishapur University of Medical Sciences, Golestan street,Ahvaz, Khozestan, Iran.
Tel: +98-9163051096
Fax: +98-611444612
E-mail: mansour3amin@gmail.com

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of HPV treatment is to eliminate signs and symptoms. Topical treatments of genital warts are numerous, including podophyllin, trichloroacetic acid, imiquimod and podofilox (podophyllotoxin) [4-6].

Podophyllin resin is derived from the rhizome of *Podophyllum peltatum*, a plant that grows wild in eastern North America, and its 25 percent solution has been used for the treatment of anogenital warts[5,7]. But it has been shown that podophyllin resin is both less effective and less cost-effective than purified podophyllotoxin, the active ingredient, and is no longer recommended as an self-application option for patient due to its widespread toxicity[8].

Components of garlic (*Allium sativum* L.) have shown antiviral effects and inhibitation of cellular proliferation of virally infected cells[9]. A clinical trial revealed that the application of garlic extract could result in the complete removal of cutaneous warts. It seems to owe to the fibrinolytic effect of garlic extract[10]. Shallomin is a pure fraction of persian shallot (*Allium hirtifolium* Boiss) extract that belongs to the genus *Allium*, which includes garlic[11]. Previous studies have shown that shallomin has antibacterial and antiviral activity with no significant adverse events[11,12].

Actually, treatments for genital warts are unlikely to be standardized due to the clinical variations presented, specific considerations in each patient, and lack of effective antiviral therapy or established disease treatment. Thus, from a clinical point of view, the clinician should have a range of options for disease treatment and employ them appropriately according to the different infected cases. The treatment modalities for genital warts vary widely and have different degrees of effectiveness. The aim of the present study was to evaluate the effects of shallomin and its comparisons with the podophyllin solution 25% in the treatment of external genital HPV warts in women. To our knowledge, it is the first randomized trial study to evaluate this natural topical remedy.

2. Materials and methods

2.1. Ethical considerations

The present study was approved by the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (ethics code: IR.AJUMS.REC.1395.662), and registered in the Iranian Registry of Clinical Trials (registration number: IRCT2017011531949N1). To collect information for this study, the research objectives were explained to each participant and written informed consent was obtained from all participants; each person had the right to choose whether to participate in the study.

2.2. Study design and data collection

A randomized controlled trial was performed in the Dermatology Department of Imam Khomeini Educational Complex hospital in Ahvaz, southwest Iran, between March 2017 and September 2017 to assess the efficacy of shallomin compared with podophyllin 25% among women who were diagnosed with HPV external genital warts by a dermatologist member of the research team. Data were collected using a demographic information questionnaire. The demographic information questionnaire was designed by the researchers. It consisted of questions about the age, weight, height, and the duration of genital wart.

2.3. Sample size estimation

We calculated a requisite study sample size of 50 patients (25 in each group) using an alpha error of 0.05 and a power of 0.80.

2.4. Inclusion and exclusion criteria

The inclusion criteria were as follows: the existence of at least a single lesion less than 2 cm in greatest diameter on the external genital area. The exclusion criteria were as follows: age under 15 years, lactating, pregnant or in postpartum period (6 weeks after delivery), having received treatment for genital warts in last three months, internal genital or anal canal warts, acute sexually transmitted disease, evidence of malignant neoplastic disease, history of previous immunosuppressive therapy or any condition associated with immunodeficiency, existence of open lesions or wounds in the area which treatment is administered.

2.5. Extraction of shallomin

The method of extraction of shallomin was adopted as previously described[10]. In short, 300 g of fresh shallot bulbs (collected from Zagros Mountains, 50 km to Dezful City, south of Iran, in spring season) were washed thoroughly in water and broken down into small pieces by an electrical grinder, soaked in 300 mL distilled water for 24 h, and filtered by Whatman filter paper No. 1 (Whatman, Camlab, Norman way, UK). The aqueous extract was mixed with ethyl acetate in a 50:50 ratio and stirred for 10 min. The upper organic layer was separated using a separating funnel and centrifuged at 5 000 rpm for 10 min. The ethyl acetate layer was then removed and transferred into a clean flask. This process was repeated 3 times, and the extracts were pooled and dried in a rota-evaporator (Heidolph, Germany) at 50 ℃. The yield from the extract was weighed and dissolved in ethanol (Merck, Germany) at a 0.5% concentration, packed in 20 mL spray bottle containers, and stored in a refrigerator at 4 ℃ until used.

2.6. Subjects and experimental protocol

A total of 2 groups (n=25 per group) of the females with external genital HPV warts who met the inclusion criteria were recruited in this study. The women were randomly allocated by a random number table into one of the two treatment groups. In the first group, shallomin has been used for treatment. The patients received treatment once a day for six weeks at home and they were assessed by a dermatologist weekly. In the second group podophyllin 25% solution (Xi'an Hao Xuan Biological Technology Co., China), was applied with a cotton wool applicator on the lesion by a

dermatologist once weekly for six weeks. Before using the drug, the surrounding of the lesion was coated with zinc oxide cream. Patients were advised to wash the place 4 h later. No treatment was dispensed for self-application at home in this group. Patients were advised to avoid sexual intercourse without condom protection during the study period. And the patients who failed to complete the treatment regimen were excluded from the analysis. Responses to the treatment were evaluated by examining the reduction in the diameter of the initial wart. Based on the rate of disappearance, and size reduction, therapeutic responses were defined in three sections: complete response (65%–100% disappearance of warts), partial response (30%–64% reduction of warts), and lack of response (<30% reduction of warts). Treatment was discontinued when all patients showed a complete response before week six. Patients who had demonstrated a complete response while noted a recurrence between ending treatment and the assessment at week 6 were asked to report to the research team. A baseline assessment was performed before the first administration of treatment at week 0, and weekly assessments were performed during weeks 1-6 to document the lesion size and disease status. The adverse events including pain, irritation, and soreness were recorded 6 weeks after treatment. In addition, the patients were evaluated 12 weeks after treatment for any possible recurrence. The detailed flow chart is shown in Figure 1.

2.7. Statistical analysis

Statistical analyses were performed using SPSSTM software version 22.0 (IBM Corporation, Armonk, NY, USA) and the results were presented as mean ± standard deviation (SD). The qualitative and quantitative variables were examined by *Chi*-square test, Fisher's exact test, Student *t*-test or its nonparametric equivalent, *i.e.*, Mann–Whitney, respectively. Normal data distribution was confirmed by the Kolmogorov-Smirnov test. All tests was considered statistically significant if the *P*-value was <0.05.

3. Result

3.1. Study population

Among the total of 50 patients who enrolled in this trial, 47 patients (23 patients in shallomin group and 24 patients in podophyllin group) completed the treatment regimen. The patients of the two treatment groups did not show statistically significant difference according to the age, body mass index and duration of warts prior to therapy (Table 1).

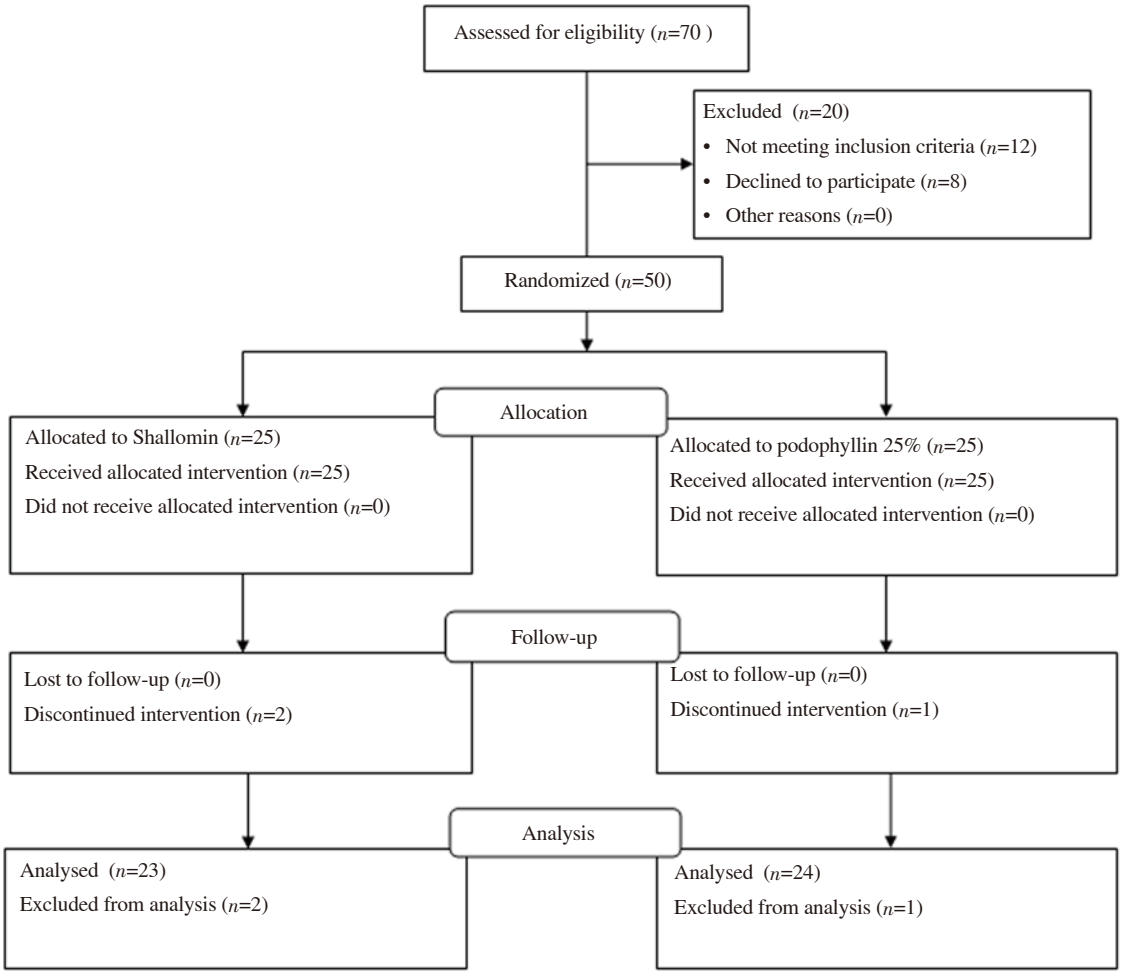

Figure 1. The detailed flow chart.

Table 1. Entry characteristics for all patients.

Characteristics	Shallomin group (*n*=23)	Podophyllin group (*n*=24)	*P*-value
Age (year)	33.26±11.36	34.00±11.56	0.826
Weight (kg)	68.47±18.34	69.95±16.39	0.772
Height (cm)	162.34±6.11	162.54±6.17	0.914
Duration of warts prior to therapy (year)	1.98±0.86	1.27±0.59	0.338

3.2. Treatment effects

Both groups showed a significant decrease in lesion size on the external genital area, 6 weeks after intervention. Among the 47 patients who completed the treatment regimen, 25 (53.1%) women completely cleared their genital warts. Shallomin and podophyllin resulted in wart clearance in 13/23 (56.5%), and 12/24 (50%) of patients, respectively. After 6 weeks of treatment with shallomin, the size of warts was significantly reduced (P<0.001).

Also, after six weeks of treatment with podophyllin, the size was significantly reduced (P<0.001). There was no significant difference between two groups in size of warts after treatment for 6 weeks (P>0.05). Major outcomes differences and adverse reactions of two regimens are shown in Table 2. According to Table 2, there was no significant difference between the two treatments in terms of patients' outcomes and adverse events of two regimens at six weeks.

Table 2. Major outcomes in the two groups at 6 weeks [*n*(%)].

Outcomes	Shallomin group (*n*= 23)	Podophyllin group (*n*= 24)	*P*-value
State of warts:			
Complete respond	13 (56.5)	12 (50.0)	0.082
Partial respond	6 (26.1)	7 (29.2)	0.430
No change	4 (17. 4)	5 (20.8)	0.362
Adverse events:			
Soreness	1 (4.3)	2 (8.3)	0.421
Pain	1 (4.3)	2 (8.3)	0.421
Irritation	1 (4.3)	3 (12.5)	0.712
No adverse events	20 (87.0)	17 (70.8)	0.864

4. Discussion

Wart treatment has always been one of the major problems for clinicians, since no sole treatment has been proved effective, so various therapeutic methods have been introduced to cope with this disease[13]. In this randomized clinical trial study which consisted of 50 women with genital warts, the effects of shallomin and podophyllin 25% solution on treating warts were compared. The results of this study confirm previous observations that none of these methods are able to completely clear genital warts. *Allium hirtifolium* Boiss, known as persian shallot, is a spice used as a traditional medicine in Iran and the Mediterranean region, whose antimicrobial properties are derived from a flavonoid active compound with the chemical formula of $C_{14}H_8O_8$ and with the proposed name of shallomin[13,14]. The results of the in vitro study showed that the raw extract of this plant has antibacterial effects against a variety of pathogenic bacteria such as methicillin-resistant *Staphylococcus aureus*[14]. Furthermore, this extract has fungicidal activity against varieties of fungus including *Aspergillus*, *Penicillium*, and *Microsporum*[15]. In a clinical trial study by Pipelzadeh *et al*, the topical lotion of shallomin 0.5% showed effective antiviral properties in treating oral herpes and preventing their progress[11].

In the present survey, the therapeutic responses of genital warts to shallomin and podophyllin 25% were considered as size reduction of warts. In clinical terms, there are three categories of complete respond (65%–100% disappearance of the warts), partial respond (30%–64% reduction of the warts), and no response (<30% reduction of the warts). Regarding the therapeutic response, the results of this study showed that shallomin caused a significant reduction in the size of warts 6 weeks after the treatment (P=0.001). Since the mean size of the genital wart at the beginning of the treatment was (2.43±1.00) mm and decrease to (1.00±0.47) mm 6 weeks after treatment with shallomin (a size reduction of 65%–100%), the therapeutic response is classified as a complete response. On the other hand, podophyllin 25% led to a complete therapeutic response, considering that it reduced the size of warts from (2.29±0.99) mm in the 1st week to (0.65±0.29) mm in the 6th week (P<0.001). In this study, the complete response to podophyllin and shallomin was 50% and 56.5%, respectively. According to the findings of the present investigation, it can be stated that shallomin can be proposed as a probable therapy for genital warts, in comparison with podophyllin. Contrary to our research, in the clinical trial study by Yaaghubi *et al*, the shallomin did not show any inhibitory effect on plane warts and could not lead to a significant decrease in the size and number of warts[13].

Compared to our survey, in the study by Stone *et al* the lower clearance rate (41%) of genital warts was observed among patients treated with podophyllin[16]. Podophyllin has been the most common therapy for genital warts in public sexually transmitted diseases in health centers because of its convenience and low cost, but low clearance rates have led to a greater tendency towards alternative therapeutic approaches such as cryotherapy, and electrosurgery[16]. Previous clinical trials revealed that clearance rates for podophyllin ranging from 23%-72% and have shown that cryotherapy and electrosurgery are superior to podophyllin produce clearance rates for genital warts ranging from 27-88 and 61-94, respectively[17]. Some previous studies disclosed that response to genital wart therapy is influenced by individual wart area, total wart area, duration, and anatomic site[16]. In our study, genital wart clearance rates did not differ by duration of warts prior to therapy in any of the treatment groups.

The results of the current study revealed that topical lotion of shallomin 0.5% in addition to its safety and easy to use, could be as effective as podophyllin in the treatment of female genital wart. The antiviral mechanisms of shalomin have not yet been well understood, and to find out more about these mechanisms, studies with more details are needed. By increasing the concentration of shalomin or its

combination with conventional anti-warts treatments, it may increase the effectiveness of its therapeutic properties, which requires more in-depth investigations.

In conclusion, despite the fact, our results showed no significant difference in the efficacy of podophyllin and shalomin extract on the treatment of female genital warts, self-application of shalomin extract was an easier method for patients than coming many times to clinics for cryotherapy. In the present study, a new regimen was used for the treatment of genital HPV warts and this is the first study using this treatment, however, more studies should be performed to compare shallomin with the other genital warts treatment methods. There was no serious adverse event in the topical application of shalomin extract.

Conflict of interest statement

The authors report no conflict of interest.

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